On Triazoles XLI [1]. Synthesis of meso-ionic [1,2,4]triazolo[5,1-*c*]thiadiazoles

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Type **6** meso-ionic [1,2,4]triazolo[5,1-*c*]thiadiazoles were synthesised by oxidation of the corresponding *N*-methyl-*N'*-(substitutedbenzal)-5-amino-3-substituted-1,2,4-triazol-1-yl)thiohydrazide (**3**) type bases or their [1,2,4]triazolo[5,1-*d*][1,2,3,6]tetrazepin-5-thion (**4**) type ring tautomers. Besides spectroscopical evidence a preparative proof of their structure was also provided. X-ray diffraction analysis of 3-methylthio-6-morpholino-1,2,4-triazolo[5,1-*c*]thiadiazole (**8**) showed quite unusual bond lengths for the N^1-S and S-C^3 bonds of the thiadiazole ring proving the meso-ionic character of these derivatives unequivocally.

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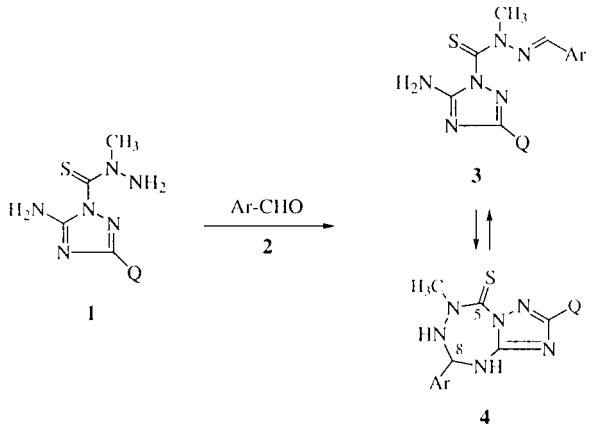
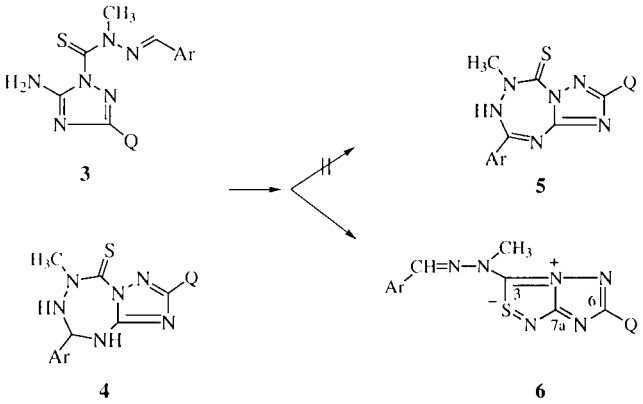
In a previous paper of this series [2] we have reported on the reaction of different *N*-methyl-3-Q-(5-amino-1,2,4-triazol-1-yl)thiohydrazides (**1**) with aromatic aldehydes (**2**) to yield depending on the solvents used for the crystallisation either the Schiff bases **3** or their [1,2,4]triazolo[1,5-*d*]-[1,2,4,6]tetrazepin-5-thione **4** ring tautomers (Scheme 1). Dissolving initially pure derivatives of either **3** or **4** in nmr solvents led to an equilibria of both tautomeric forms.

Scheme 1



Derivatives **3** and **4** possessed valuable biological activity [3,4]. However such compounds that are not stable in solution are highly disadvantageous in pharmaceutical chemistry. Therfore we wanted to stabilise the tetrahydro [1,2,4]triazolo[1,5-*d*][1,2,4,6]tetrazepin-5-thione ring system of compounds **4** by oxidation, with ferric chloride, to the derivatives **5** that are not able to undergo ring-chain tautomeric equilibria. However, both, the oxidation of derivatives **3** and **4** led instead of the expected derivatives **5** to the formation of [1,2,4]triazolo[5,1-*c*]thiadiazoles (**6**) being present in intramolecular meso-ionic form (Scheme 2). Derivatives **6** represent a novel ring system.

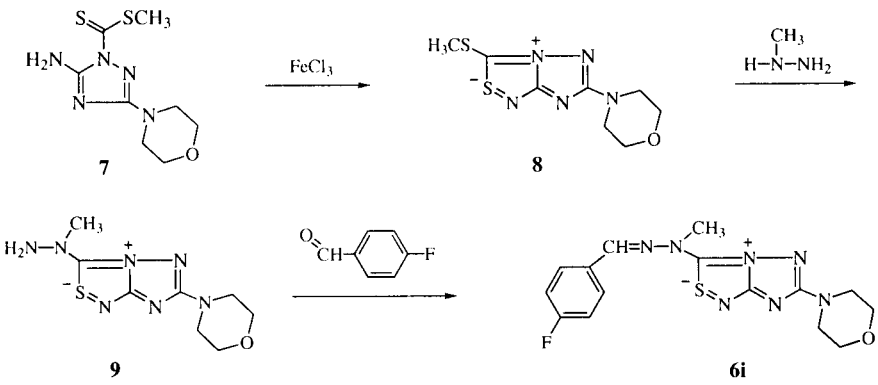
Scheme 2



The structure of derivatives **6** is consistent with the benzalhydrazo CH group present appearing between 7.78-8.53 ppm in the pmr and between 135.5-148.8 ppm in the cmr. It is worth mentioning that the steric effect of the *ortho* substituents of the benzal moiety caused regardless of their identity an upfield shift of the CH carbon atoms in the cmr. The intramolecular meso-ionic structure of the [1,2,4]triazolo[5,1-*c*]thiadiazole ring system of derivatives **6** is in very good agreement with the very similar chemical shifts of the carbon atoms 3, 6 and 7a appearing at 172.7-179.1, 165.3-166.6 and 159.4-163.7 ppm, respectively.

The intramolecular meso-ionic character of the newly built in [1,2,4]triazolo[5,1-*c*]thiadiazole ring system was also proved by X-ray diffraction analysis of **8** (Scheme 3, Figure 1, Table 1) showing that the sulphur atom of the thiadiazole moiety is neither in S^{IV}, nor in S^{II} oxidation form. The meso-ionic character of **8** is in accordance with the quite unusual bond lengths of the N^1-S^2 and S^2-C^3 bonds, being of the value of 1.655Å and 1.704Å (selected bond distances and angles are listed in Table 2). They can be compared with the expected [5-7] N=S and S=C bond

Scheme 3



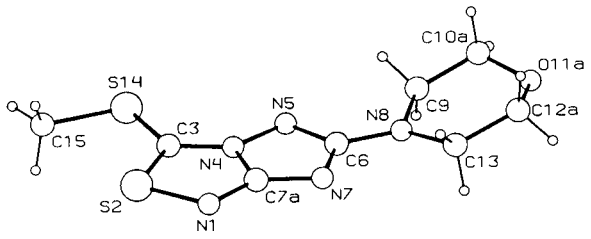


Fig. 1a

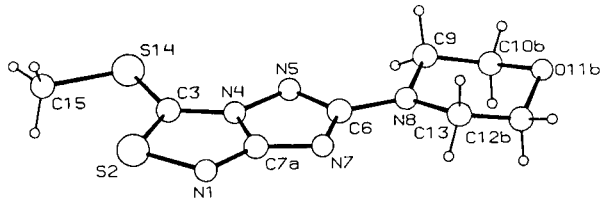


Fig 1b

Perspective view of **8** (Fig. 1a.: conformer a, Fig 1b.: conformer b).

lengths of the N=S=C moiety being of 1.535-1.603Å and 1.646-1.662Å, respectively.

The structure of derivatives **6** was also proved by a preparative method. Thus methyl (5-amino-3-morpholino-1,2,4-triazol-1-yl)dithiocarbonate (**7**) [8] was oxidised with ferric chloride to 3-methylthio-6-morpholino-1,2,4-triazolo[5,1-*c*][1,2,4]thiadiazole (**8**) (Scheme 3) that was converted with methylhydrazine to 3-(1-methylhydrazo)-6-morpholino-1,2,4-triazolo[5,1-*c*][1,2,4]thiadiazole (**9**). The reaction of **9** with 4-fluorobenzaldehyde led to the expected 6-morpholino-3-[1-methyl-2-(4-fluorobenzal)-hydrazo]-1,2,4-triazolo[5,1-*c*][1,2,4]thiadiazole (**6i**) obtained previously by the oxidation of *N*-methyl-*N'*-(4-fluorobenzal)-(5-amino-3-morpholino-1,2,4-triazol-5-yl)thiohydrazide (**3i**).

Table 1

Fractional atomic coordinates and equivalent isotropic displacement parameters (Å x 10^3) for non-hydrogen atoms in 8. Estimated standard deviations are in parenthesis, U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor. The site occupation factor for atoms C10a, O11a, C12a is 0.4, whereas for atoms C10b, O11b, C12b is 0.6

Atom	x/a	y/b	z/c	U_{eq}
N1	-0.0074(4)	-0.2752(3)	-0.0175(4)	45(1)
S2	-0.0880(1)	-0.1991(1)	-0.1498(1)	42(1)
C3	0.0322(4)	-0.1002(3)	-0.1442(4)	29(1)
N4	0.1307(3)	-0.1277(2)	-0.0395(3)	27(1)
N5	0.2517(3)	-0.0825(2)	0.0187(3)	30(1)
C6	0.2929(4)	-0.1578(3)	0.1225(4)	32(1)
N7	0.2125(3)	-0.2455(3)	0.1352(4)	38(1)
C7A	0.1095(4)	-0.2255(3)	0.0310(3)	33(1)
N8	0.4117(3)	-0.1458(3)	0.2108(4)	39(1)
C9	0.4906(7)	-0.0488(5)	0.2102(7)	78(3)
C10a	0.5797(13)	-0.0168(11)	0.3363(14)	52(5)
C10b	0.6225(8)	-0.0611(8)	0.2710(10)	60(4)
O11a	0.6373(9)	-0.0945(8)	0.4214(11)	70(4)
O11b	0.6467(6)	-0.1245(5)	0.4076(7)	65(2)
C12a	0.5492(18)	-0.1820(14)	0.4505(16)	82(8)
C12b	0.5779(9)	-0.2222(9)	0.3852(11)	70(4)
C13	0.4465(8)	-0.2197(5)	0.3332(7)	101(2)
S14	0.0300(1)	0.0167(1)	-0.2463(1)	37(1)
C15	-0.1295(5)	-0.0008(4)	-0.3576(5)	43(1)

Table 2

Selected bond distances (() and angles (°).

N1 -S2	1.655(4)	N4 -C7A	1.398(4)
N1 -C7A	1.337(5)	N5 -C6	1.354(4)
S2 -C3	1.704(4)	C6 -N7	1.359(5)
C3 -N4	1.322(4)	C6 -N8	1.350(5)
C3 -S14	1.718(4)	N7 -C7A	1.329(5)
N4 -N5	1.369(4)	S14 -C15	1.783(5)
S2 -N1 -C7A	107.4(5)	N5 -C6 -N7	118.6(5)
N1 -S2 -C3	96.5(3)	N5 -C6 -N8	120.4(6)
S2 -C3 -N4	106.7(4)	N7 -C6 -N8	120.9(6)
S2 -C3 -S14	128.7(4)	C6 -N7 -C7A	101.4(5)
N4 -C3 -S14	124.5(5)	N1 -C7A -N4	114.8(5)
C3 -N4 -C7A	114.5(5)	N4 -C7A -N7	110.1(5)
N5 -N4 -C7A	110.4(4)	C3 -S14 -C15	99.0(3)
N4 -N5 -C6	99.4(4)		

EXPERIMENTAL

Melting points were determined on a Koffler-Boëtius micro apparatus and are not corrected. The infrared spectra were obtained as potassium bromide pellets using a Perkin-Elmer 577 spectrophotometer. The pmr and cmr measurements were performed using a Varian WM-250 instrument. The ms spectra were taken with a KRATOS MS 25 RFA double focusing instrument in EI and CI mode.

General Method for the Preparation of Derivatives **6**.

Method A

To a solution of 0.1 mole of the corresponding Schiff's base **3** in 115 ml of acetic acid a solution of 73 g (0.45 mole) of ferric chloride in 100 ml of water was added and refluxed with stirring for an appropriate time (see in brackets in the individual experiments). After cooling 1500 ml of water were added to the mixture, stirred for 30 minutes and the crystals that precipitated were filtered off.

Method B

To a solution of 0.1 mole of the corresponding Schiff's base **3** in 250 ml of acetic acid a solution of 146 g (0.9 mole) of ferric chloride in 175 ml of water was added and refluxed with stirring for an appropriate time (see in brackets in the individual experiments). After cooling 2000 ml of water were added to the mixture, stirred for 30 minutes and the crystals that precipitated were filtered off.

6-Methylthio-3-[1-methyl-2-(4-fluorobenzal)hydrazo]-1,2,4-triazolo[5,1-*c*][1,2,4]thiadiazole (**6a**).

Method A starting from 21.1 g (0.065 mole) of *N*-methyl-*N'*-(4-fluorobenzal)-(5-amino-3-methylthio-1,2,4-triazol-1-yl)thiohydrazide (**3a**) [2] (reaction time 15 minutes) was followed. Yield: 9.05 g (43%) of **6a** that after recrystallisation from dimethylformamide melted at 248-250°; ir: ν C=N = 1628, 1609 and 1569 cm^{-1}; pmr (DMSO-d_6): δ, ppm 2.58 (s, 3H, SCH_3), 4.07 (s, 3H, NCH_3), 7.36 [t (J = 8.8 Hz), 2H, PhH-2,6], 7.85 [dd (J = 8.8 and 3.0 Hz), 2H, PhH-3,5], 8.38 (s, 1H, CH); cmr (DMSO-d_6): δ, ppm 13.2 (SCH_3), 34.0 (NCH_3), 116.3 [d (J = 22.3 Hz), PhC-3',5'], 129.4 [d (J = 2.7 Hz), PhC-1'], 130.0 [d (J = 8.9 Hz), PhC-2',6'], 145.0 (CH), 161.7 (C-7a), 164.0 [d (J = 248.9 Hz), PhC-4'), 165.7 (C-6), 176.3 (C-3).

Anal. Calcd. for $C_{12}H_{11}FN_6S_2$ (mw 322.39): C, 44.71; H, 3.44; F, 5.89; N, 26.07; S, 19.89. Found: C, 44.85; H, 3.56; F, 5.68; N, 25.99; S, 19.98.

6-Methylthio-3-[1-methyl-2-(4-chlorobenzal)hydrazo]-1,2,4-triazolo[5,1-*c*][1,2,4]thiadiazole (**6b**).

Method B starting from 13.6 g (0.04 mole) of *N*-methyl-*N'*-(4-chlorobenzal)-(5-amino-3-methylthio-1,2,4-triazol-1-yl)thiohydrazide (**3b**) [2] (reaction time 30 min) was followed. Yield: 8.65 g (64%) of **6b** that after recrystallisation from dimethylformamide melted at 278-280°; ir: ν C=N = 1632, 1606 and 1569 cm^{-1}; pmr (deuteriochloroform): δ, ppm 2.65 (s, 3H, SCH_3), 4.17 (s, 3H, NCH_3), 7.45[d (J = 8.5 Hz), 2H, PhH-2,6], 7.67 [d (J = 8.5 Hz), 2H, PhH-3,5], 7.89 (s, 1H, CH); cmr (DMSO-d_6): δ, ppm 13.0 (SCH_3), 33.9 (NCH_3), 107.9 (PhC-3',5'), 129.2 (PhC-2',6'), 131.6 (PhC-1'), 135.5 (PhC-4'), 144.7 (CH), 161.9 (C-7a), 165.9 (C-6), 179.1 (C-3).

Anal. Calcd. for $C_{12}H_{11}ClN_6S_2$ (mw 338.84): C, 42.54; H, 3.27; Cl, 10.46; N, 24.80; S, 18.93. Found: C, 42.57; H, 3.48; Cl, 10,43; N, 24.68; S, 19.03.

6-Methylthio-3-[1-methyl-2-(2,6-dichlorobenzal)hydrazo]-1,2,4-triazolo[5,1-*c*][1,2,4]thiadiazole (**6c**).

Method B starting from 7.5 g (0.02 mole) of *N*-methyl-*N'*-(2,6-dichlorobenzal)-(5-amino-3-methylthio-1,2,4-triazol-1-yl)thiohydrazide (**3c**) [2] (reaction time 4 hours) was followed. Yield: 5.61 g (75%) of **6c** that after recrystallisation from dimethylformamide melted at 228-230°; ir: ν C=N = 1628, 1596 and 1553 cm^{-1}; pmr (deuteriochloroform): δ, ppm 2.65 (s, 3H, SCH_3), 4.19 (s, 3H, NCH_3), 7.29 [t (J = 7.6 Hz), 1H, PhH-4'], 7.43 [dd (J = 7.6 and 0.8 Hz), 2H, PhH-3,5], 8.20 (s, 1H, CH); cmr (DMSO-d_6): δ, ppm 13.0 (SCH_3), 33.6 (NCH_3), 128.2 (PhC-1'), 129.5 (PhC-3',5'), 131.2 (PhC-4'), 134.1 (PhC-2',6'), 140.5 (CH), 162.3 (C-7a), 166.1 (C-6), 178.3 (C-3).

Anal. Calcd. for $C_{12}H_{10}Cl_2N_6S_2$ (mw 373.29): C, 38.61; H, 2.70; Cl, 19.00, N, 22.51; S, 17.18. Found: C, 38.58; H, 2.88; Cl, 19.12; N, 22.40; S, 17.24.

6-Methylthio-3-[1-methyl-2-(4-dimethylaminobenzal)hydrazo]-1,2,4-triazolo[5,1-*c*][1,2,4]thiadiazole (**6d**).

Method A starting from 17.85 g (0.051 mole) of *N*-methyl-*N'*-(4-dimethylaminobenzal)-(5-amino-3-methylthio-1,2,4-triazol-1-yl)thiohydrazide (**3d**) [2] (reaction time 15 minutes) was followed. Yield: 5.88 g (33%) of **6d** that after recrystallisation from dimethylformamide melted at 248-250°. Extracting the water-acetic acid containing mother liquor with chloroform a further crop (4.87 g) of the title product was obtained increasing the yield to 60%; ir: ν C=N = 1632, 1611 and 1589 cm^{-1}; pmr (deuteriochloroform): δ, ppm 2.63 (s, 3H, SCH_3), 3.05 (s, 6H, NCH_3), 4.06 (s, 3H, NCH_3), 6.67 [d (J = 9.0 Hz), 2H, PhH-3',5'], 7.53 [d (J = 9.0 Hz), 2H, PhH-2',6'], 7.79 (s, 1H, CH); cmr (DMSO-d_6): δ, ppm 13.7 (SCH_3), 33.0 (NCH_3), 40.0 [$N(CH_3)_2$], 111.7 (PhC-3',5'), 119.7 (PhC-1'), 129.4 (PhC-2',6'), 144.4 (CH), 152.4 (PhC-4'), 161.9 (C-7a), 166.5 (C-6), 179.1 (C-3).

Anal. Calcd. for $C_{14}H_{17}N_7S_2$ (mw 347.47): C, 48.39; H, 4.93; N, 28.22; S, 18.46. Found: C, 48.30; H, 5.09; N, 28.05; S, 18.44.

6-Methylthio-3-[1-methyl-2-(4-carbamoylmethylenoxybenzal)-hydrazo]-1,2,4-triazolo[5,1-*c*][1,2,4]thiadiazole (**6e**).

Method B starting from 14.8 g (0.039 mole) of *N*-methyl-*N'*-(4- carbamoylmethylenoxybenzal)-(5-amino-3-methylthio-1,2,4-triazol-1-yl)thiohydrazide (**3e**) [2] (reaction time 30 minutes) was followed. Yield: 7.12 g (48%) of **6e** that after recrystallisation from dimethylformamide melted at 261-264°; ir: ν C=O = 1687 cm^{-1}, ν C=N = 1637, 1579 and 1512 cm^{-1}; pmr (DMSO-d_6): δ, ppm 2.56 (s, 3H, SCH_3), 4.04 (s, 3H, NCH_3), 4.75 (s, 2H, CH_2), 7.03 [d (J = 8.8 Hz), 2H, PhH-3',5'), 7.72 [d (J = 8.8 Hz), 2H, PhH-2',6'], 8.29 (s, 1H, CH); cmr (DMSO-d_6): δ, ppm 13.0 (SCH_3), 33.6 (NCH_3), 64.6 (CH_2), 115.0 (PhC-3',5'), 125.6 (PhC-1'), 129.2 (PhC-2',6'), 145.6 (CH), 160.0 (PhC-4'), 161.6 (C-7a), 165.8 (C-6), 169.7 (C=O), 175.9 (C-3).

Anal. Calcd. for $C_{14}H_{15}N_7O_2S_2$ (mw 377.45): C, 44.55; H, 4.01; N, 25.98; S, 16.99. Found: C, 44.40; H, 4.09; N, 26.05; S, 17.11.

6-Morpholino-3-(1-methyl-2-benzalhydrazo)-1,2,4-triazolo[5,1-*c*]-[1,2,4]thiadiazole (**6f**).

Method B starting from 2.07 g (0.006 mole) of *N*-methyl-*N'*-benzal-(5-amino-3-morpholino-1,2,4-triazol-1-yl)thiohydrazide (**3f**) [2] (reaction time 15 minutes) was followed. Yield: 1.00 g (49%) of **6f** that after recrystallisation from methanol melted at 257-259°; ir: ν C=N = 1639 and 1528 cm^{-1}; pmr (deuteriochloroform): δ, ppm

3.61 [dd (J = 5.0 and 4.4 Hz), 4H, NCH_2], 3.78 [dd (J = 5.0 and 4.4 Hz), 4H, OCH_2], 4.12 (s, 3H, NCH_3), 7.45 [m, 3H, PhH-3', 4', 5'], 7.71 [m, 2H, PhH-2',6'], 7.87 (s, 1H, CH); cmr (deuteriochloroform): δ, ppm 33.1 (NCH_3), 45.6 (NCH_2), 66.5 (OCH_2), 127.6 (PhC-2',6'), 129.0 (PhC-3',5'), 131.0 (PhC-4'), 132.7 (PhC-1'), 142.4 (CH), 159.9 (C-7a), 165.8 (C-6), 175.1 (C-3).

Anal. Calcd. for $C_{15}H_{17}N_7OS$ (mw 343.41): C, 52.46; H, 4.99; N, 28.55; S, 9.34. Found: C, 52.35; H, 5.11; N, 28.60; S, 9.28.

6-Morpholino-3-[1-methyl-2-(2-fluorobenzal)hydrazo]-1,2,4-triazolo[5,1-*c*][1,2,4]thiadiazole (**6g**).

Method B starting from 10.1 g (0.0278 mole) of *N*-methyl-*N'*-(2-fluorobenzal)-(5-amino-3-morpholino-1,2,4-triazol-1-yl)thiohydrazide (**3g**) [9] (reaction time 2 hours) was followed. Yield: 8.6 g (86%) of **6g** that after recrystallisation from dimethylformamide melted at 247-248°; ir: ν C=N = 1632, 1604 and 1531 cm^{-1}; pmr (deuteriochloroform): δ, ppm 3.60 [dd (J = 5.1 and 4.4 Hz), 4H, NCH_2], 3.77 [dd (J = 5.1 and 4.4 Hz), 4H, OCH_2], 4.11 (s, 3H, NCH_3), 7.12-7.42 (m, 3H, PhH- 4', 5', 6'), 7.90 [dt (J = 6.0 and 1.5 Hz), 1H, PhH-3'], 8.09 (s, 1H, CH); cmr (deuteriochloroform): δ, ppm 33.2 (NCH_3), 45.6 (NCH_2), 66.6 (OCH_2), 116.0 [d (J = 20.7 Hz), PhC-3'], 120.7 [d (J = 9.6 Hz), PhC-1'], 124.8 [d (J = 3.3 Hz), PhC-6'], 126.8 [d (J = 1.6 Hz), PhC-5'], 132.5 [d (J = 8.4 Hz), PhC-4'], 135.5 [d (J = 5.4 Hz), CH], 159.7 (C-7a), 161.5 [d (J = 252.2 Hz), PhC-2'], 166.0 (C-6), 175.2 (C-3).

Anal. Calcd. for $C_{15}H_{16}FN_7OS$ (mw 361.40): C, 49.85; H, 4.46; F, 5.26; N, 27.13; S, 8.87. Found: C, 50.04; H, 4.70; F, 5.23; N, 27.15; S, 8.84.

6-Morpholino-3-[1-methyl-2-(3-fluorobenzal)hydrazo]-1,2,4-triazolo[5,1-*c*][1,2,4]thiadiazole (**6h**).

Method B starting from 9.2 g (0.0253 mole) of *N*-methyl-*N'*-(3-fluorobenzal)-(5-amino-3-morpholino-1,2,4-triazol-1-yl)thiohydrazide (**3h**) [10] (reaction time 2 hours) was followed. Yield: 7.3 g (80%) of **6h** that after recrystallisation from dimethylformamide melted at 258-260°; ir: ν C=N = 1634, 1598 and 1553 cm^{-1}; pmr (deuteriochloroform): δ, ppm 3.62 [m, 4H, NCH_2], 3.79 [m, 4H, OCH_2], 4.13 (s, 3H, NCH_3), 7,36 (m, 1H, PhH-5'), 7.55-7.68 (m, 2H, PhH- 4', 6'), 7.62 (m, 1H, PhH-2'), 8.29 (s, 1H, CH); cmr (DMSO-d_6): δ, ppm 33.7 (NCH_3), 45.3 (NCH_2), 65.8 (OCH_2), 113.4 [d (J = 22.9 Hz), PhC-2'], 117.6 [d (J = 22.1 Hz), PhC-4'], 123.8 (PhC-6'), 131.2 [d (J = 8.6 Hz), PhC-5'], 135.4 [d (J = 5.9 Hz), PhC-1'], 143.4 (CH), 159.7 (C-7a), 162.5 [d (J = 244.3 Hz), PhC-3'], 165.4 (C-6), 174.6 (C-3).

Anal. Calcd. for $C_{15}H_{16}FN_7OS$ (mw 361.40): C, 49.85; H, 4.46; F, 5.26; N, 27.13; S, 8.87. Found: C, 49.81; H, 4.55; F, 5.33; N, 27.03; S, 8.80.

6-Morpholino-3-[1-methyl-2-(4-fluorobenzal)hydrazo]-1,2,4-triazolo[5,1-*c*][1,2,4]thiadiazole (**6i**).

Method A starting from 21.1 g (0.058 mole) of *N*-methyl-*N'*-(4-fluorobenzal)-(5-amino-3-morpholino-1,2,4-triazol-1-yl)thiohydrazide (**3i**) [11] (reaction time 30 minutes) was followed. Yield: 9.05 g (43%) of **6i** that after recrystallisation from dimethylformamide melted at 272-274°; ir: ν C=N = 1613 and 1553 cm^{-1}; pmr (deuteriochloroform): δ, ppm 3.61 [dd (J = 5.2 and 4.3 Hz), 4H, NCH_2], 3.79 [dd (J = 5.2 and 4.3 Hz), 4H, OCH_2], 4.11 (s, 3H, NCH_3), 7.15 [t (J = 8.6 Hz), 2H, PhH-2',6'), 7.71 (m, 2H, PhH-3',5'), 7.84 (s, 1H, CH); cmr (deuteriochloroform): δ, ppm 33.2 (NCH_3), 45.7 (NCH_2), 66.6 (OCH_2), 116.4 [d (J = 22.3 Hz), PhC-3',5'], 129.2 [d (J = 2.7 Hz), PhC-1'], 129.7 [d (J = 8.8 Hz), PhC-2',6'], 141.2 (CH), 162.5 (C-7a), 163.6 [d (J = 257.9 Hz), PhC-4'], 166.6 (C-6), 175.4 (C-3).

Anal. Calcd. for $C_{15}H_{16}FN_7OS$ (mw 361.40): C, 49.85; H, 4.46; F, 5.26; N, 27.13; S, 8.87. Found: C, 49.77; H, 4.62; F, 5.18; N, 27.10; S, 8.76.

6-Morpholino-3-[1-methyl-2-(2-chlorobenzal)hydrazo]-1,2,4-triazolo[5,1-*c*][1,2,4]thiadiazole (**6j**).

Method B starting from 10.9 g (0.0286 mole) of *N*-methyl-*N'*-(2-chlorobenzal)-(5-amino-3-morpholino-1,2,4-triazol-1-yl)thiohydrazide (**3j**) [12] (reaction time 2 hours) was followed. Yield 8.5 g (79%) of **6j** that after recrystallisation from dimethylformamide melted at 263-265°; ir: ν C=N = 1632, 1601 and 1532 cm^{-1}; pmr (deuteriochloroform): δ, ppm 3.62 [dd (J = 5.1 and 4.4 Hz), 4H, NCH_2], 3.79 [dd (J = 5.1 and 4.4 Hz), 4H, OCH_2], 4.14 (s, 3H, NCH_3), 7.38 (m, 3H, PhH- 4', 5', 6'), 7.98 (m, 1H, PhH-3'), 8.26 (s, 1H, CH); cmr (deuteriochloroform): δ, ppm 33.3 (NCH_3), 45.7 (NCH_2), 66.3 (OCH_2), 127.4 (PhC-3',5'), 130.1, 130.3 (PhC-1',6'), 131.7 (PhC-4'), 134.6 (PhC-2'), 138.8 (CH), 159.7 (C-7a), 166.0 (C-6), 175.3 (C-3).

Anal. Calcd. for $C_{15}H_{16}ClN_7OS$ (mw 377.86): C, 47.68; H, 4.27; Cl, 9.38; N, 25.95; S, 8.49. Found: C, 47.60; H, 4.36; Cl, 9.31; N, 26.13; S, 8.44.

6-Morpholino-3-[1-methyl-2-(3-chlorobenzal)hydrazo]-1,2,4-triazolo[5,1-*c*][1,2,4]thiadiazole (**6k**).

Method B starting from 6.20 g (0.0163 mole) of *N*-methyl-*N'*-(3-chlorobenzal)-(5-amino-3-morpholino-1,2,4-triazol-1-yl)thiohydrazide (**3k**) [13] (reaction time 2 hours) was followed. Yield: 4.5 g (73%) of **6k** that after recrystallisation from dimethylformamide melted at 261-263°; ir: ν C=N = 1629, 1588 and 1551 cm^{-1}; pmr (deuteriochloroform): δ, ppm 3.46 [dd (J = 5.1 and 4.3 Hz), 4H, NCH_2], 3.67 [dd (J = 5.1 and 4.3 Hz), 4H, OCH_2], 4.06 (s, 3H, NCH_3), 7.55 (m, 2H, PhH-5',6'), 7.75-7.80 (m, 2H, PhH-2',4'), 8.30 (s, 1H, CH); cmr (DMSO-d_6): δ, ppm 33.6 (NCH_3), 45.2 (NCH_2), 65.6 (OCH_2), 125.8, 126.7 (PhC-2',4'), 130.2, 130.8 (PhC-1',6'), 133.7 (PhC-5'), 135.0 (PhC-3'), 143.2 [d(J = 5.4 Hz), CH], 159.5 (C-7a), 165.3 (C-6), 174.5 (C-3).

Anal. Calcd. for $C_{15}H_{16}ClN_7OS$ (mw 377.86): C, 47.68; H, 4.27; Cl, 9.38; N, 25.95; S, 8.49. Found: C, 47.78; H, 4.41; Cl, 9.27; N, 25.90; S, 8.53.

6-Morpholino-3-[1-methyl-2-(4-chlorobenzal)hydrazo]-1,2,4-triazolo[5,1-*c*][1,2,4]thiadiazole (**6l**).

Method B starting from 1.90 g (0.005 mole) of *N*-methyl-*N'*-(4-chlorobenzal)-(5-amino-3-morpholino-1,2,4-triazol-1-yl)thiohydrazide (**3l**) [2] (reaction time 15 minutes) was followed. Yield: 1.18 g (62%) of **6l** that after recrystallisation from a 3:2 mixture of dioxane and water melted at 289-291°; ir: ν C=N = 1639, 1606 and 1554 cm^{-1}; pmr (trifluoroacetic acid): δ, ppm 3.80 (m, 4H, NCH_2), 4.15 (s, 3H, NCH_3), 4.21 (m, 4H, OCH_2), 7.51 [d (J = 8.4 Hz), 2H, PhH-2',6'), 7.76 [d (J = 8.4 Hz), 2H, PhH-3',5'], 8.23 (s, 1H, CH).

Anal. Calcd. for $C_{15}H_{16}ClN_7OS$ (mw 377.86): C, 47.68; H, 4.27; Cl, 9.38; N, 25.95; S, 8.49. Found: C, 47.78; H, 4.41; Cl = 9.27; N, 25.90; S, 8.53.

6-Morpholino-3-[1-methyl-2-(2,4-dichlorobenzal)hydrazo]-1,2,4-triazolo[5,1-*c*][1,2,4]thiadiazole (**6m**).

Method B starting from 12.6 g (0.0304 mole) of *N*-methyl-*N'*-(2,4-dichlorobenzal)-(5-amino-3-morpholino-1,2,4-triazol-1-yl)-

thiohydrazide (**3m**) [14] (reaction time 2 hours) was followed. Yield 9.4 g (75%) of **6m** that after recrystallisation from dimethylformamide melted at 267-269°; ir: ν C=N = 1628, 1591 and 1546 cm^{-1}; pmr (deuteriochloroform): δ, ppm 3.61 [dd (J = 4.7 and 4.2 Hz), 4H, NCH_2], 3.78 [dd (J = 4.7 and 4.2 Hz), 4H, OCH_2], 4.14 (s, 3H, NCH_3), 7.34 [dd (J = 8.5 and 2.1 Hz), 1H, PhH-5'), 7.45 [d (J = 2.1 Hz), 1H, PhH-3'), 7.90 [d (J = 8.5 Hz), 1H, PhH-6'), 8.18 (s, 1H, CH); cmr (deuteriochloroform): δ, ppm 33.4 (NCH_3), 45.6 (NCH_2), 66.5 (OCH_2), 128.0, 128.2 and 128.9 (PhC-3', 5', and 6'), 129.9 (PhC-1'), 134.9 (PhC-2'), 137.2 (PhC-4'), 137.6 (CH), 159.4 (C-7a), 166.0 (C-6), 175.3 (C-3).

Anal. Cald. for $C_{15}H_{15}Cl_2N_7OS$ (mw 412.30): C, 43.70; H, 3.67; Cl, 17.20; N, 23.78; S, 7.78. Found: C, 43.61; H, 3.75; Cl, 17.27; N, 23.80; S, 7.63.

6-Morpholino-3-[1-methyl-2-(2,6-dichlorobenzal)hydrazo]-1,2,4-triazolo[5,1-*c*][1,2,4]thiadiazole (**6n**) by oxidation of *N*-methyl-*N'*-(2,6-dichlorobenzal)-(5-amino-3-morpholino-1,2,4-triazol-1-yl)thiohydrazide (**3n**).

Method B starting from 4.14 g (0.01 mole) of *N*-methyl-*N'*-(2,6-dichlorobenzal)-(5-amino-3-morpholino-1,2,4-triazol-1-yl)-thiohydrazide (**3n**) [2] (reaction time 15 minutes) was followed. Yield: 2.90 g (70%) of **6n** that after recrystallisation from dimethylformamide melted at 248-251°; ir: ν C=N = 1645, 1592 and 1544 cm^{-1}; pmr (deuteriochloroform): δ, ppm 3.62 [dd (J = 5.1 and 4.4 Hz), 4H, NCH_2], 3.80 [dd (J = 5.1 and 4.4 Hz), 4H, OCH_2], 4.16 (s, 3H, NCH_3), 7.26 [d (J = 8.2 Hz), 1H, PhH-4'), 7.42 [d (J = 8.2 Hz), 2H, PhH-3', 5'), 7.90 [d (J = 8.5 Hz), 1H, PhH-6'), 8.13 (s, 1H, CH); cmr (deuteriochloroform): δ, ppm 32.9 (NCH_3), 45.7 (NCH_2), 66.6 (OCH_2), 128.5 (PhC-3', 5'), 129.5 (PhC-4'), 130.8 (PhC-1'), 135.3 (PhC-2',6'), 137.6 (CH), 160.0 (C-7a), 166.0 (C-6), 175.4 (C-3).

Anal. Cald. for $C_{15}H_{15}Cl_2N_7OS$ (mw 412.30): C, 43.70; H, 3.67; Cl, 17.20; N, 23.78; S, 7.78. Found: C, 43.74; H, 3.77; Cl, 17.12; N, 23.68; S, 7.73.

6-Morpholino-3-[1-methyl-2-(2,6-dichlorobenzal)hydrazo]-1,2,4-triazolo[5,1-*c*][1,2,4]thiadiazole (**6n**) by oxidation of 8-(2,6-dichlorophenyl)-6-methyl-2-morpholino-5,6,7,8-tetrahydro-1,2,4-triazolo[1,5-*d*][1,2,4,6]tetrazepine-5(9*H*)-thione (**4n**).

Method B starting from 1.4 g (0.00338 mole) of 8-(2,6-dichlorophenyl)-6-methyl-2-morpholino-5,6,7,8-tetrahydro-1,2,4-triazolo[1,5-*d*][1,2,4,6]tetrazepine-5(9*H*)-thione (**4n**) [2] (reaction time 2 hours) was followed. Yield: 1.02 g (73%) of **6n** that after recrystallisation from dimethylformamide melted at 248-250°. The product is identical (ir, mixed mp) with that of **6n** obtained in the previous experiment.

6-Morpholino-3-[1-methyl-2-(2-nitrobenzal)hydrazo]-1,2,4-triazolo[5,1-*c*][1,2,4]thiadiazole (**6o**).

Method B starting from 11.20 g (0.0287 mole) of *N*-methyl-*N'*-(2-nitrobenzal)-(5-amino-3-morpholino-1,2,4-triazol-1-yl)thiohydrazide (**3o**) [15] (reaction time 2 hours) was followed. Yield 9.4 g (84%) of **6o** that after recrystallisation from dimethylformamide melted at 251-253°; ir: ν C=N = 1634, 1590, 1560 and 1527 cm^{-1}; pmr (deuteriochloroform): δ, ppm 3.63 [dd (J = 5.1 and 4.3 Hz), 4H, NCH_2], 3.80 [dd (J = 5.1 and 4.3 Hz), 4H, OCH_2], 4.18 (s, 3H, NCH_3), 7.63 [dd (J = 7.8 and 1.5 Hz), 1H, PhH-3'], 7.77 [dd (J = 7.3 and 1.4 Hz), 1H, PhH-6']), 8.11 (m, 2H, PhH-3',4'), 8.54 (s, 1H, CH); cmr (deuteriochloroform): δ, ppm 33.7 (NCH_3), 45.7 (NCH_2), 66.6 (OCH_2), 125.2 (PhC-3'), 127.9, 128.8 (PhC-4',6'), 131.0 (PhC-1'), 134.0 (PhC-5'), 138.1 (CH), 148.2 (PhC-2'), 159.5 (C-7a), 166.1 (C-6), 175.5 (C-3).

Anal. Calcd. for $C_{15}H_{16}N_8O_3S$ (mw 388.41): C, 46.39; H, 4.15; N, 28.85; S, 8.26. Found: C, 46.42; H, 4.26; N, 29.02; S, 8.17.

6-Morpholino-3-[1-methyl-2-(3-nitrobenzal)hydrazo]-1,2,4-triazolo[5,1-*c*][1,2,4]thiadiazole (**6p**).

Method B starting from 11.20 g (0.0287 mole) of *N*-methyl-*N'*-(3-nitrobenzal)-(5-amino-3-morpholino-1,2,4-triazol-1-yl)thiohydrazide (**3p**) [2] (reaction time 2 hours) was followed. Yield 6.4 g (57%) of **6p** that after recrystallisation from dimethylformamide melted at 283-285°; ir: ν C=N = 1642, 1562 and 1530 cm^{-1}; pmr (deuteriochloroform): δ, ppm 3.66 [t (J = 4.9 Hz), 4H, NCH_2], 3.79 [t (J = 4.9 Hz), 4H, OCH_2], 4.17 (s, 3H, NCH_3), 7.67 [dd (J = 8.3 and 7.8 Hz), 1H, PhH-5'], 7.94 (m, 1H, PhH-2'), 8.10 [d (J = 7.8 Hz), 1H, PhH-4'], 8.30 [d (J = 8.3 Hz), 1H, PhH-6'], 8.45 (s, 1H, CH); cmr (deuteriochloroform): δ, ppm 33.6 (NCH_3), 45.7 (NCH_2), 66.5 (OCH_2), 122.8 (PhC-2'), 125.4 (PhC-4'), 130.2 (PhC-6'), 132.3 (PhC-5'), 139.8 (PhC-1'), 148.8 (CH), 150.1 (PhC-3'), 157.9 (C-7a), 165.4 (C-6), 172.7 (C-3).

Anal. Calcd. for $C_{15}H_{16}N_8O_3S$ (mw 388.41): C, 46.39; H, 4.15; N, 28.85; S, 8.26. Found: C, 46.22; H, 4.16; N, 28.70; S, 8.20.

6-Morpholino-3-[1-methyl-2-(4-nitrobenzal)hydrazo]-1,2,4-triazolo[5,1-*c*][1,2,4]thiadiazole (**6r**).

Method B starting from 5.60 g (0.0144 mole) of *N*-methyl-*N'*-(4-nitrobenzal)-(5-amino-3-morpholino-1,2,4-triazol-1-yl)thiohydrazide (**3r**) [2] (reaction time 2 hours) was followed. Yield 4.33 g (77%) of 6-morpholino-3-[1-methyl-2-(4-nitrobenzal)hydrazo]-1,2,4-triazolo[5,1-*c*][1,2,4]thiadiazole (**6r**) that after recrystallisation from dimethylformamide melted at 271-273°; ir: ν C=N = 1635, 1581, 1561 and 1523 cm^{-1}; pmr (deuteriochloroform): δ, ppm 3.64 [dd (J = 5.1 and 4.4 Hz), 4H, NCH_2], 3.79 [dd (J = 5.1 and 4.4 Hz), 4H, OCH_2], 4.18 (s, 3H, NCH_3), 7.87 [d (J = 8.8 Hz), 2H, PhH-3',5'], 7.91 (s, 1H, CH), 8.31 = [d (J = 8.8 Hz), 2H, PhH-2',6']); cmr (DMSO-d_6): δ, ppm 34.2 (NCH_3), 45.4 (NCH_2), 65.9 (OCH_2), 124.5 (PhC-3',5'), 128.5 (PhC-2',6'), 139.2 (PhC-1'), 142.5 (CH), 148.4 (PhC-4'), 159.7 (C-7a), 165.6 (C-6), 174.8 (C-3).

Anal. Calcd. for $C_{15}H_{16}N_8O_3S$ (mw 388.41): C, 46.39; H, 4.15; N, 28.85; S, 8.26. Found: C, 46.48; H, 4.31; N, 28.73; S, 8.27.

6-Morpholino-3-[1-methyl-2-(3,4,5-trimethoxybenzal)hydrazo]-1,2,4-triazolo[5,1-*c*][1,2,4]thiadiazole (**6s**).

Method A starting from of 1.72 g (0.00434 mole) of *N*-methyl-*N'*-(3,4,5-trimethoxybenzal)-(5-amino-3-morpholino-1,2,4-triazol-1-yl)thiohydrazide (**3s**) [2] (reaction time 10 minutes) was followed. As the reaction mixture did not crystallise after the addition of water it was extracted with 2 x 50 ml portions of chloroform, the combined chloroform layers were extracted with water, dried over anhydrous sodium sulfate, filtered and evaporated *in vacuo* to dryness. The residue (1.6 g) was passed through a short silica gel column (eluent chloroform) to yield after evaporation of the appropriate fractions 1.0 g (53%) of **6s** that after recrystallisation from dimethylformamide melted at 257-259°; ir: ν C=N = 1633, 1593 and 1546 cm^{-1}; pmr (deuteriochloroform): δ, ppm 3.59 [dd (J = 5.2 and 4.3 Hz), 4H, NCH_2], 3.77 [dd (J = 5.1 and 4.4 Hz), 4H, OCH_2], 3.90 (s, 3H, OCH_3-4'), 3.92 (s, 6H, OCH_3-3',5'), 4.10 (s, 3H, NCH_3), 6.93 (s, 2H, PhH-2',6']), 7.78 (s,

1H, CH); cmr (deuteriochloroform): δ, ppm 33.1 (NCH_3), 45.5 (NCH_2), 56.1 (OCH_3-3',5'), 60.9 (OCH_3-4'), 66.4 (OCH_2), 104.7 (PhC-2',6'), 127.9 (PhC-1'), 140.8 (PhC-4'), 142.1 (PhC-3',5'), 153.6 (CH), 159.6 (C-7a), 165.7 (C-6), 174.9 (C-3).

Anal. Calcd. for $C_{18}H_{23}N_7O_4S$ (mw 433.49): C, 49.87; H, 5.35; N, 22.62; S, 7.40. Found: C, 49.70; H, 5.30; N, 22.71; S, 7.44.

6-Morpholino-3-[1-methyl-2-(4-carbamoylmethylenoxybenzal)-hydrazo]-1,2,4-triazolo[5,1-*c*][1,2,4]thiadiazole (**6t**).

Method B starting from 3.78 g (0.009 mole) of *N*-methyl-*N'*-(4-carbamoylmethylenoxybenzal)-(5-amino-3-morpholino-1,2,4-triazol-1-yl)thiohydrazide (**3t**) [2] (reaction time 15 minutes) was followed. Yield 2.1 g (56%) of **6t** that after recrystallisation from dimethylformamide melted at 293-294°; ir: ν C=O = 1681 cm^{-1}, ν C=N = 1640, 1598 and 1556 cm^{-1}; pmr (DMSO-d_6): δ, ppm 3.45 [t (J = 4.8 Hz), 4H, NCH_2], 3.67 [t (J = 4.8 Hz), 4H, OCH_2], 4.06 (s, 3H, NCH_3), 4.51 (s, 2H, 4'-OCH_2), 7.10 [d (J = 9.0 Hz), 2H, PhH-3',5'], 7.75 [d (J = 9.0 Hz), 2H, PhH-2',6']), 8.25 (s, 1H, CH); MS (EI): M^+ = 416.

Anal. Calcd. for $C_{17}H_{20}N_8O_3S$ (mw 416.47): C, 49.03; H, 4.84; N, 26.91; S, 7.70. Found: C, 49.15; H, 4.99; N, 26.83; S, 7.66.

3-Methylthio-6-morpholino-1,2,4-triazolo[5,1-*c*][1,2,4]thiadiazole (**8**).

Method B starting from 77.8 g (0.3 mole) of methyl (5-amino-3-morpholino-1,2,4-triazol-1-yl)dithiocarbonate (**7**) [8] (reaction time 30 minutes) was followed. Yield 60.2 g (78%) of **8** that after recrystallisation from acetonitrile melted at 199-201°; ir: ν C=N = 1551 cm^{-1}; pmr (DMSO-d_6): δ, ppm 2.87 (s, 3H, SCH_3), 3.49 [dd (J = 5.1 and 4.4 Hz), 4H, NCH_2], 3.66 [dd (J = 5.1 and 4.4 Hz), 4H, OCH_2]; cmr (DMSO-d_6): δ, ppm 15.7 (SCH_3), 45.2 (NCH_2), 65.6 (OCH_2), 156.7 (C-7a), 166.4 (C-6), 176.0 (C-3).

Anal. Calcd. for $C_8H_{11}N_5OS_2$ (mw 257.34): C, 37.34; H, 4.31; N, 27.21; S, 24.92. Found: C, 37.40; H, 4.42; N, 27.13; S, 25.03.

3-(1-Methylhydrazo)-6-morpholino-1,2,4-triazolo[5,1-*c*]-[1,2,4]thiadiazole (**9**).

To a mixture of 32.25 g (0.125 mole) of 3-methylthio-6-morpholino-1,2,4-triazolo[5,1-*c*][1,2,4]thiadiazole (**8**) and 500 ml of methanol 8.05 ml (9.2 g, 0.2 mole) of methyl hydrazine were added and the mixture was refluxed with stirring for 2 hours. After cooling the crystals that precipitated were filtered off to yield 17.25 g (34%) of 3-(1-methylhydrazo)-6-morpholino-1,2,4-triazolo[5,1-*c*][1,2,4]thiadiazole that after recrystallisation from 2-propanol melted at 226-228°; ir: ν C=N = 1675, 1615 and 1548 cm^{-1}; pmr (deuteriochloroform): δ, ppm 3.55 [dd (J = 5.1 and 4.5 Hz), 4H, NCH_2], 3.76 [dd (J = 5.1 and 4.5 Hz), 4H, OCH_2], 3.83 (s, 3H, NCH_3), 4.60 (bs, 2H, NH_2); pmr (DMSO-d_6): δ, ppm 3.38 [dd (J = 5.1 and 4.4 Hz), 4H, NCH_2], 3.64 [dd (J = 5.1 and 4.4 Hz), 4H, OCH_2)], 3.79 (s, 3H, NCH_3), 5.92 (bs, 2H, NH_2); cmr (DMSO-d_6): δ, ppm 41.4 (NCH_3), 45.3 (NCH_2), 65.6 (OCH_2), 163.7 (C-7a), 165.7 (C-6), 174.0 (C-3).

Anal. Calcd. for $C_8H_{13}N_7OS$ (mw 255.30): C, 37.64; H, 5.13; N, 38.40; S, 12.56. Found: C, 37.70; H, 5.23; N, 38.28; S, 12.50.

6-Morpholino-3-[1-methyl-2-(4-fluorobenzal)hydrazo]-1,2,4-triazolo[5,1-*c*][1,2,4]thiadiazole (**6i**) from 3-(1-methylhydrazo)-6-morpholino-1,2,4-triazolo[5,1-*c*][1,2,4]thiadiazole (**9**) and 4-fluorobenzaldehyde.

To a mixture of 1.28 g (0.005 mole) of 3-(1-methylhydrazo)-6-morpholino-1,2,4-triazolo[5,1-*c*][1,2,4]thiadiazole (**9**) and 40 ml of ethanol 0.64 ml (0.74 g = 0.006 mole) of 4-fluorobenzaldehyde were added and the mixture refluxed with stirring for 2 days. After cooling the crystals that precipitated were filtered off to yield 1.15 g (64%) of **6i** that after recrystallisation from methanol melted at 271-274°. The product is identical (ir, mixed mp) with that of **6i** obtained by oxidation of *N*-methyl-*N'*-(4-fluorobenzal)-(5-amino-3-morpholino-1,2,4-triazol-5-yl)thiohydrazide (**3i**).

Crystal structure analysis of **8**.

The analysis is based on the following data: $C_8H_{11}N_5OS$, Fw = 257.34, monoclinic, space group $P2_1/c$ Z = 4, T = 293K, a = 9.933(1), b = 12.342(1), c = 9.155(1) Å, β = 97.43(1)°, V = 1112.9(3) $Å^3$, crystal size 0.20 x 0.35 x 0.50 mm D_c = 1.54 $g.cm^{-3}$, F(000) = 472. The intensities of 2424 reflections (2407 independent, 2041 observed with $I > 3\sigma(I)$) were measured on an Enraf-Nonius CAD-4 diffractometer ($\theta/2\theta$ scan $3° < 2\theta < 150°$) with graphite monochromated CuK_α (λ = 1.54184 Å) radiation. An absorption correction was made by programme DIFABS [16] t_{min} = 0.474, t_{max} = 0.999. The structure was solved by direct methods and refined in anisotropic approximation by full matrix least squares versus F_0 to 0.066 (wR = 0.088) terminated by the positional disorder of three non-hydrogen atoms C10, O11, C12 of the morpholino moiety. The ratio between the conformer a/b was found to be 4:6. The hydrogen positions were located from assumed geometries but were not refined.

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[9] Compound **3g** was prepared according to the General Procedure described in [2]. Yield 84%, mp 154-156° (ethanol).

[10] Compound **3h** was prepared according to the General Procedure described in [2]. Yield 60%, mp 148-150° (ethanol).

[11] Compound **3i** was prepared according to the General Procedure described in [2]. Yield 79%, mp 160-162° (ethanol).

[12] Compound **3j** was prepared according to the General Procedure described in [2]. Yield 84%, mp 171-173° (ethanol).

[13] Compound **3k** was prepared according to the General Procedure described in [2]. Yield 62%, mp 145-147° (ethanol).

[14] Compound **3m** was prepared according to the General Procedure described in [2]. Yield 88%, mp 193-195° (ethanol).

[15] Compound **3o** was prepared according to the General Procedure described in [2]. Yield 73%, mp 212-214° (ethanol).

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